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(54) Title: 10-ARYL-11-*H*BENZO [*b*]FLUORENE DERIVATIVES AND ANALOGS FOR MEDICINAL USE

(57) Abstract: The invention provides for a non-steroidal compound having the formula [I], wherein R^c and $'R^c$ are OH, optionally independently etherified or esterified; Z is $-CH_2-$ or $-CH_2CH_2-$; R^1 is H, halogen, CF_3, or (1C-4C)alkyl; R^2, R^3 and R^4 are independently H, halogen, $-CF_3$, $-OCF_3$, (1C-8C)Alkyl, hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-8C)alkyl, $-O(CH_2)_mX$, wherein X is halogen or phenyl and m = 2-4; $-O(CH_2)_mNR_aR_b$, $-S(CH_2)_mNR_aR_b$ or $-(CH_2)_mNR_aR_b$, wherein m = 2-4 and R_a, R_b are independently (1C-8C)alkyl, (2C-8C)alkenyl, (2C-8C)alkynyl, or aryl, optionally substituted with halogen, $-CF_3$, $-OCF_3$, -CN, $-NO_2$, -OH, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl or R_a and R_b form a 3-8 membered ring structure, optionally substituted with halogen, $-CF_3$, $-OCF_3$, -CN, $-NO_2$, hydroxy, hydroxy(1C-4C)alkyl, (1C-8C)alkoxy, aryloxy, (1C-8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl. The compounds can be used for the preparation of a medicine, in particular for use in estrogen-receptor-related treatments.

10-ARYL-11*H*-BENZO[*b*]FLUORENE DERIVATIVES AND ANALOGS FOR MEDICINAL USE

The invention relates to a non-steroidal compound with affinity for estrogen receptors and to a method for selective estrogen receptor modulation (SERM) with such a compound and to the use of such a compound for the manufacture of a medicine for estrogen-receptor related treatments.

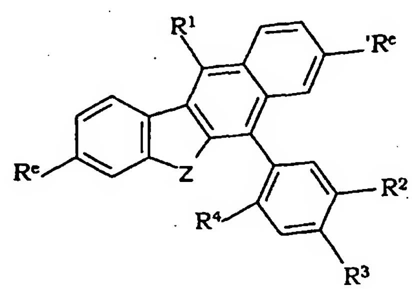
Compounds with affinity for estrogen receptors have found long-standing utility in the treatment of a variety of medical indications and in regimes for contraceptive purposes. Despite the long history of the field there still is a need for more effective, safer and more economical compounds than the existing ones. This need is the more pressing in view of advancement in health care in other areas, which has led to an increasingly longer life span. This is in particular a problem for women for whom the decline in estrogenic hormones at menopause is drastic and has negative consequences for bone strength and cardiovascular functions. For the control or prevention of estrogen sensitive tumor growth, compounds are needed which are antagonists, partial antagonists or tissue selective agonists for estrogen receptors.
The discovery of subtypes of estrogen receptors, there being an α-subtype (ERα) and a β-subtype (ERβ) of such receptors (Mosselman et al., <u>FEBS Letters</u> vol. 392 (1996) pp. 49-53 as well as EP -A- 0 798 378), offers the possibility to influence one particular subtype of those two receptors more selectively, immanently resulting in more effective treatments or treatments with less side effects. Since these receptors have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress, making it possible to provide a more selective treatment in estrogen-receptor related medical treatments, such as those for contraception and for treatment of menopausal complaints, osteoporosis, and estrogen dependent tumour control, with a lower burden of estrogen-related side-effects.

This invention pertains to non-steroidal estrogenic compounds with a 10-aryl-11*H*-benzo[*b*]fluorene or a 7-aryl-5,6-dihydrobenz[*a*]anthracene

skeleton. Compounds with a 10-phenyl-11*H*-benzo[*b*]fluorene skeleton are described as products from enediyne thermocyclisation [Schmittel, M., *Z. Naturforsch., B: Chem. Sci.* (1998), **53**, 1015-1020] and from [4+2] cycloaddition reactions of diarylacetylenes [Rodriguez, D., *Org. Lett.* (2000), **2**, 1497-1500], but no medicinal activity of these compounds is known. Indeno[1,2-*g*]quinolines with interactions with nuclear receptors are disclosed in WO 96 19458. Despite the keen interest in compounds with affinity for the estrogen receptor, new compounds with a 10-aryl-11*H*-benzo[*b*]fluorene or 7-aryl-5,6-dihydrobenz[*a*]anthracene skeleton and affinity for the estrogen receptor cannot be learnt from these documents.

The present invention resides in the finding that compounds with an unsaturated or partially unsaturated four-ring skeleton with hydroxyl substitutions at specific locations, i.e. 2,8-dihydroxy-10-aryl-11*H*-benzo[*b*]fluorene and 3,9-dihydroxy-7-aryl-5,6-dihydro-benz[*a*]anthracene, possess surprisingly high antagonism for ERβ. Some of these compounds also show ERα antagonism or ERα agonism.

Specifically, the invention provides non-steroidal compounds having the formula 1



Formula 1

wherein:

R^e and 'R^e are OH, optionally independently etherified or esterified;

Z is $-CH_2-$ or $-CH_2CH_2-$;

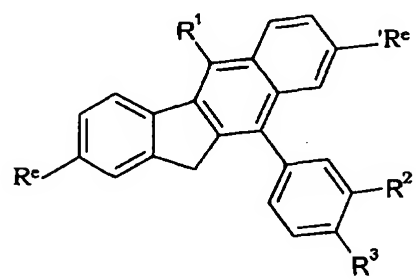
R^1 is H, halogen, CF_3 , or (1C-4C)alkyl;

R^2, R^3 and R^4 are independently H, halogen, $-CF_3$, $-OCF_3$, (1C-8C)Alkyl, hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-8C)alkyl, $-O(CH_2)_mX$, wherein X is halogen or phenyl and m = 2-4; -

$O(CH_2)_mNR_aR_b$, $-S(CH_2)_mNR_aR_b$ or $-(CH_2)_mNR_aR_b$, wherein m = 2-4 and wherein R_a, R_b are independently (1C-8C)alkyl, (2C-8C)alkenyl, (2C-8C)alkynyl, or aryl, optionally substituted with halogen, $-CF_3$, $-OCF_3$, -CN, $-NO_2$, -OH, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl or R_a and R_b form a 3-8 membered ring structure, optionally substituted with halogen, $-CF_3$, $-OCF_3$, -CN, $-NO_2$, hydroxy, hydroxy(1C-4C)alkyl, (1C-8C)alkoxy, aryloxy, (1C-8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl.

Preferred compounds of the invention can be obtained by selecting $-CH_2-$ for Z and hydrogen for R^4 in formula 1. For R^1 it is preferred to select compounds having H, halogen or CF_3. Compounds with R^1 in formula 1 is halogen, whereby chlorine is most preferred, are particularly potent and selective for the ERβ.

Another embodiment of the invention is a non-steroidal compound with a 10-Aryl-11*H*-benzo[*b*]fluorene skeleton having the formula 2



Formula 2

wherein:

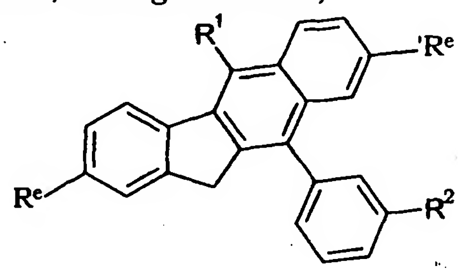
R^e and $'R^e$ are OH, optionally independently etherified or esterified;

R^1 is H, halogen or CF_3;

R^2 and R^3 are independently H, halogen, $-CF_3$, $-OCF_3$, (1C-8C)Alkyl, hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-8C)alkyl, $-O(CH_2)_mNR_aR_b$, $-S(CH_2)_mNR_aR_b$ or $-(CH_2)_mNR_aR_b$, wherein m = 2-4 and R_a, R_b are independently (1C-8C)alkyl, (2C-8C)alkenyl, (2C-8C)alkynyl, or aryl, optionally substituted with halogen, $-CF_3$, $-OCF_3$, -CN, $-NO_2$, -OH, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-

8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl or R_a and R_b form a 3-8 membered ring structure, optionally substituted with halogen, $-CF_3$, $-OCF_3$, -CN, $-NO_2$, hydroxy, (1C-8C)alkoxy, aryloxy, (1C-8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl.

For compounds, having formula 3,



Formula 3

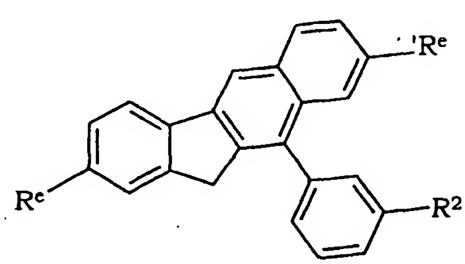
it is preferred to select those in which

R^e and $'R^e$ are OH, optionally independently etherified or esterified;

R^1 is H, halogen, CF_3;

R^2 is $-O(CH_2)_mNR_aR_b$, wherein m = 2-3 and R_a, R_b are independently (1C-5C)alkyl or (3C-5C)alkenyl, optionally substituted with OH or methoxy, or R_a and R_b form a 4-7 membered ring structure selected from the list: azetidine, pyrrolidine, 3-pyrroline, piperidine, piperazine, tetrahydropyridine, morpholine, thiomorpholine, thiazolidine, homopiperidine, tetrahydroquinoline and 6-azabicyclo[3.2.1]octane, which 4-7 membered ring structure can optionally be substituted with OH, methoxy, acetyl, carboxylate, (1C-3C)alkyl, phenyl, benzyl, and phenylethyl.

In particular, a very effective compound is made available by this invention by selecting a compound having formula 4:



Formula 4

wherein:

R^e and $'R^e$ are OH, optionally independently etherified or esterified;

R^2 is (3C-6C)alkyloxy, $-O(CH_2)_mX$ (wherein X is halogen or phenyl and m = 2-3), or $-O(CH_2)_mNR_aR_b$,(wherein m = 2-3), whereby R_a, R_b are independently (1C-5C)alkyl or (3C-5C)alkenyl, optionally substituted with OH or methoxy, or R_a and R_b form a 4-7 membered ring structure selected from the list: azetidine, pyrrolidine, 3-pyrroline, piperidine, piperazine, tetrahydropyridine, morpholine, thiomorpholine, thiazolidine, homopiperidine, tetrahydroquinoline and 6-azabicyclo[3.2.1]octane, which 4-7 membered ring structure can optionally be substituted with OH, hydroxy(1C-2C)alkyl, methoxy, acetyl, carboxylate, (1C-3C)alkyl, phenyl, benzyl, and phenylethyl.

In those cases that the compound in formulas 1-4 contain a basic amine function, the compound may be used as a free base or as a pharmaceutically acceptable salt such as hydrochloride, acetate, oxalate, tartrate, citrate, phosphate, maleate or fumarate.

The ester and ether compounds in the collection of compounds according to the invention often have activity as prodrug. A prodrug is defined as being a compound which converts in the body of a recipient to a compound as defined by the formulas 1 to 4 and to the free hydroxyl compounds of the above defined compounds. Preferred ester and ether prodrugs are carboxylic acid esters or alkyl ethers on one or both hydroxyl groups, and more preferred prodrugs are (2C-6C)carboxylic acid esters, such as esters of (iso)butanoic acid, or (1C-4C) alkyl ethers. In general, the hydroxy groups can for example be substituted by alkyl*oxy, alkenyl*oxy, acyl*oxy, aroyloxy, alk*oxycarbonyloxy, sulfonyl groups or phosphate groups, whereby the carbon chain length of the groups denoted with an asterisk (*) is not considered to be sharply delimited, while aroyl generally will comprise a phenyl, pyridinyl or pyrimidyl, which groups can have substitutions customary in the art, such as alkyl*oxy, hydroxy, halogen, nitro, cyano, and (mono-, or dialkyl*-)amino. The length of the alkyl, alkenyl and acyl groups is selected depending on the desired properties of the prodrugs, whereby

the longer chained prodrugs with for example lauryl or caproyl chains are more suitable for sustained release and depot preparations. It is known that such substituents spontaneously hydrolyse or are enzymatically hydrolysed to the free hydroxyl substituents on the skeleton of the compound. Such prodrugs will have biological activity comparable to the compounds to which they are converted in the body of the recipients. The active compound to which a prodrug is converted is called the parent compound. The onset of action and duration of action as well as the distribution in the body of a prodrug may differ from such properties of the parent compound.

Substitution variants of the compounds of the present invention are possible for similar use. A substitution variant is defined to be a compound which comprises in its molecular structure the structure as defined by the formula I. The skilled person inspecting the group of compounds provided by the present invention will immediately understand that modification by a substituent to the skeleton can yield a compound with similar biological activity as the compound without this particular substituent. It is common practise in the art to test such substitution variants for the expected biological activity so that it is a routine skill to obtain useful substitution variants of compounds according to the invention.

Other terms used in this description have the following meaning:

alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, octyl, capryl, or lauryl;

alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;

alkynyl is a branched or unbranched alkynyl group, such as ethynyl and propynyl;

halogen refers to fluorine, chlorine, bromine and iodine;

aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphtyl or pyridinyl; a monocyclic ring with 6 atoms is preferred for use;

a ring system or structure is referring to a chemical group in which all atoms are involved in formed rings, which rings can be saturated or (partially) unsaturated and comprise C, O, S or N atoms;
aroyl is arylcarbonyl such as a benzoyl group;
alkanoyl means a formyl or alkylcarbonyl group such as formyl, acetyl and propanoyl;
acyl is a (substituent-)carbonyl group, such as an aroyl or alkanoyl;
carboxyl is a –COOH substituent, making the compond an organic acid;
carboxylate is an ester or salt of a carboxyl substituent.

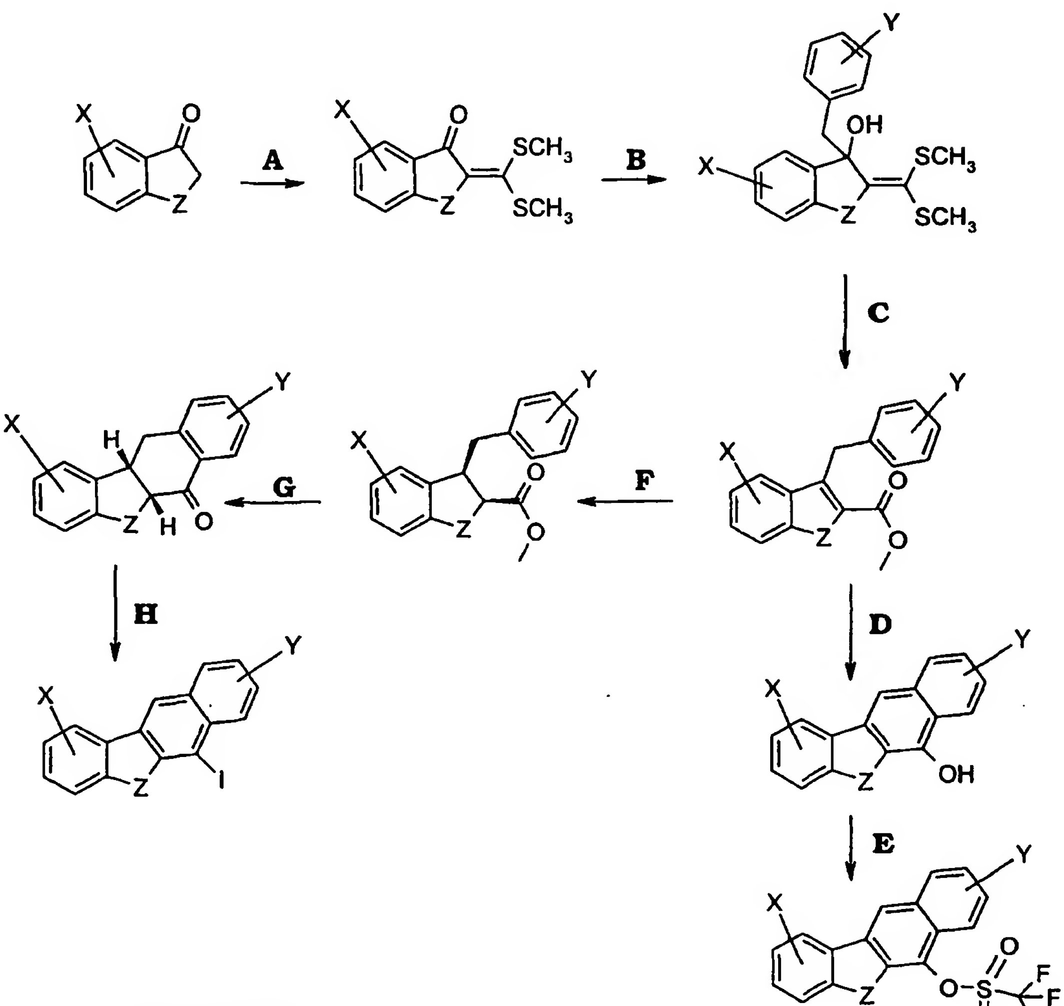
The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms.

The estrogen-receptor affinity profile of the compounds according to the present invention, makes them suitable for use in estrogen-receptor related medical treatments, in the sense that these compounds are improved anti-estrogens, partial anti-estrogen, partial estrogens or selective (partial) (anti-)estrogens. Estrogen-receptor related medical treatments specifically named are those for contraception or for treatment or prevention of benign prostate hypertrophy, cardiovascular disorders, menopausal complaints, osteoporosis, estrogen dependent tumour control or central nervous system disorders such as depression or Alzheimer's disease. In particular those compounds which have selective affinity for the ERβ receptor are suitable for estrogen-receptor related medical treatments under diminished estrogen-related side-effects. This is most desirable when these compounds are used in the treatment of osteoporosis, cardiovascular disorders and central nervous system disorders such as depression or Alzheimer's disease. Selective blockade of ERβ-receptors with compounds of this invention can be used to prevent and reduce malignent tumor growth and hyperplasias. The receptor selectivity helps to effectuate tissue selectivity. Those tissues rich in ERβ-receptors can be protected by ERβ-receptor antagonists from the risk of stimulation of growth by estrogenic agonists. The latter can be of endogenous origin or from exogenous origine when administered during estrogenic treatment, for example for hormone replacement after menopause. Tissues that can benefit from protection in view of the

presence of ERβ-receptors are prostate, testes (human), lung, colon and endometrium. In particular, endometrium proliferation can be reduced by ERβ antagonists of the invention.

The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the schemes and examples can be used.

Scheme 1. A general procedure that can be used to prepare compounds of the invention

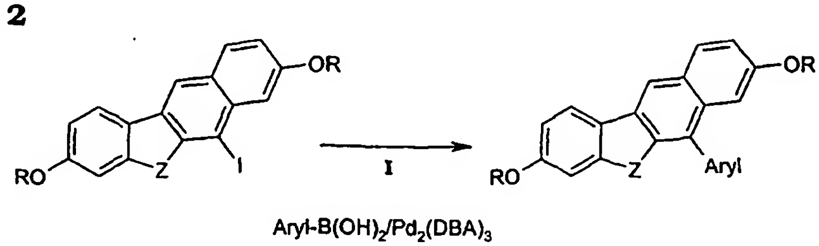


$Z = CH_2$ or CH_2CH_2

$X,Y = OCH_3$

, occasionally accompanied by other substituents

Scheme 2



R is protecting group

With reference to scheme 1, the benzofluorene ($Z=CH_2$) and the benzanthracene ($Z= CH_2CH_2$) skeleton can be assembled in an identical manner. In step **A** adequately substituted indanones or tetralones are treated with CS_2 under appropriate basic conditions to introduce a dithioketene function (in fact serving as a carboxylate equivalent), after which procedure reaction with an organometallic derivative of a substituted benzylhalide (preferably a Grignard derivative) in step **B**, followed by alcoholysis (step **C**) leads to an α,β-unsaturated ester. At this stage an acid catalyzed cyclization (step **D**) immediately leads to the phenolic benzofluorene (or benzanthracene). Conversion of this into a reactive intermediate (like triflate) in step **E** allows the introduction of the desired functionalities (like aryl groups, carboxylates etc) by means of known organometallic techniques.
If the mentioned α,β-unsaturated ester is first hydrogenated in step **F** prior to cyclization (step **G**), the indicated ketones become available. They may be easily converted into the aromatic iodide in step **H**. These, under circumstances may be more reactive than the afore-mentioned triflates and provide valuable alternatives for functionalization (step **I** in scheme 2).
Ester prodrugs can be made by esterification of compounds with free hydroxyl groups by reaction with appropriate acyl chlorides in pyridine. Free dihydroxy compounds having formula 1 can be made by hydrolysis of ether precursors.

The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro *et al*, *Remmington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing). Suitable auxiliaries are made available in e.g. the Handbook of Pharmaceutical Excipients (2nd Edition, Editors A. Wade and P.J. Weller; American Pharmaceutical Association; Washington; The Pharmaceutical Press; London, 1994). The mixture of the compounds according to the invention and the pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the

compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

Furthermore, the invention relates to the use of the non-steroidal compound according to the invention for the manufacture of a medicament for estrogen-receptor related treatments and treatment of estrogen-receptor related disorders such as peri- and/or post-menopausal complaints. Thus the invention also pertains to the medical indications of peri- and/or post-menopausal (climacteric) complaints and osteoporosis, i.e. a method of treatment in the field of hormone replacement therapy (HRT), comprising the administration to a patient, being a woman, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Further, the invention relates to the use of the non-steroidal compound according to the invention in the manufacture of a medicament having contraceptive activity. Thus the invention also pertains to the medical indication of contraception, i.e. a method of contraception comprising the administration to a subject, being a woman or a female animal, of a progestogen and an estrogen as is customary in the field, wherein the estrogen is a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Finally the invention relates to the use of the non-steroidal compound for the manufacture of a medicament having selective estrogenic and/or

anti-estrogenic activity, such a medicament being generally suitable in the area of HRT (hormone replacement therapy).

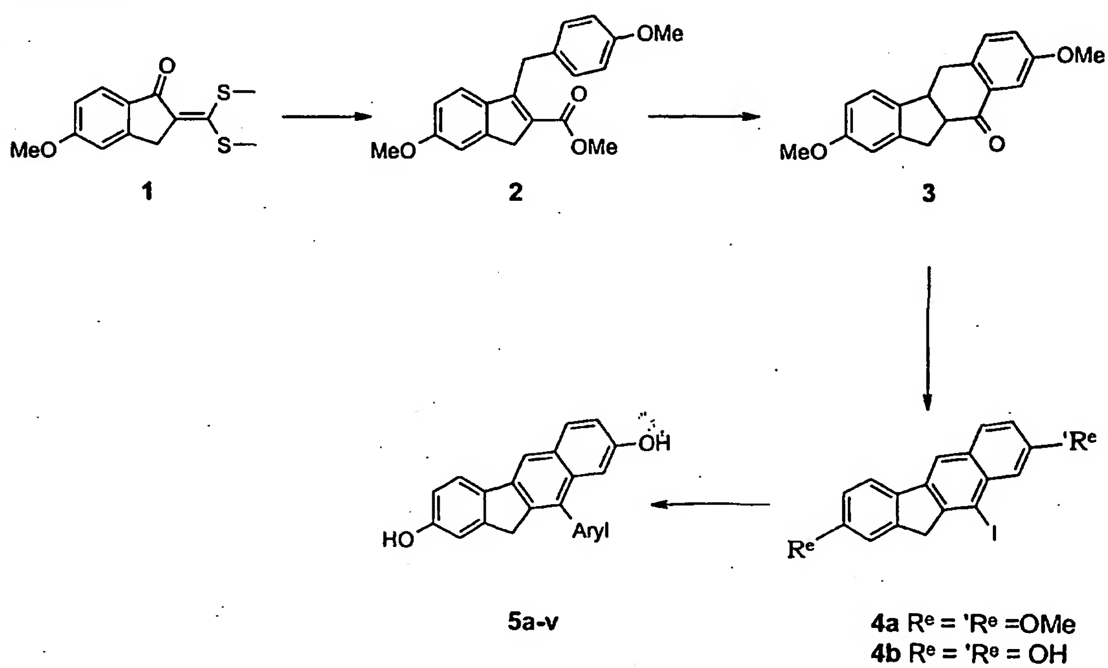
The dosage amounts of the present compounds will be of the normal order for estrogenic compounds, e.g. of the order of 0.01 to 100 mg per administration.

The invention is further illustrated hereinafter with reference to some unlimitative examples and the corresponding formula schemes referred to. Compounds are identified by numbers (in bold letter type) with reference to the corresponding numbers in the schemes. Abbreviations used in the schemes: Me is methyl, Bn is benzyl, ph is phenyl, aryl represents the substituted phenyl as in formula 1.

EXAMPLES

Example 1

Scheme 3



Preparation of precursor 10-iodo-2,8-dihydroxy-11H-benzo[b]fluorene ***(4b)***. 59 ml 4-methoxybenzyl-magnesium chloride (0.2 M in diethyl ether) was added to **1** [J.V. Ram and M. Nath, *Indian J. Chem. Sect.B*; **34**, 416-422 (1995)] (11.6 mmol) in 70 ml THF at 0°C and the reaction mixture was stirred for 0.5 hour at 20°C. The mixture was poured into saturated aq. NH_4Cl, extracted with diethyl ether and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by chromatography on silica gel (heptane/ethyl acetate). The pure fractions were concentrated and the material obtained was taken up in 95 ml methanol and treated with $BF_3.Et_2O$ (28 mmol). After 0.5 hour the temperature was raised to 65°C and after 0.5 hour the reaction mixture was poured into water, extracted with CH_2Cl_2 and the organic layer washed with $NaHCO_3$ (aq). The extract was dried over $MgSO_4$, concentrated and the residue was recrystallised from methanol to afford pure **2** in 45% yield (Rf = 0.48 heptane/ethyl acetate (3:2)).

A mixture of **2** (5 mmol) and palladium on carbon (10% Pd (w/w), 300 mg) in 120 ml ethanol/acetic acid (5:1) was stirred under an atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration and the filtrate was concentrated.

The residue was dissolved in methanesulfonic acid and stirred at 90°C for 15 minutes after which the mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$(aq) and dried over $MgSO_4$. Chromatography on silica gel (heptane/ethyl acetate) gave pure **3** in 85% yield. (Rf = 0.49 heptane/ethyl acetate (2:1)); MP 96-98°C.

The compound **3** (0.34 mmol) was dissolved in ethanol and 1 ml hydrazine monohydrate was added. After 4 hours refluxing, water was added and the hydrazone was extracted with CH_2Cl_2. The organic layer was washed with water, dried and concentrated. The residue was taken up in 1.5 ml triethylamine and 0.2 g iodine in 0.7 ml THF was added at 0°C. After 1 hour the reaction mixture was diluted with toluene, poured into ice water and extracted with toluene. The organic layer was washed with 1N HCl and saturated $NaHCO_3$(aq), dried over $MgSO_4$ and concentrated. The residue was dissolved in 8 ml m-xylene/toluene (2:1) palladium on carbon (10% w/w, 100 mg) was added and the mixture was heated at 125°C for 2 hours. After cooling the catalyst was filtered off, the filtrate was concentrated and the residue was purified on silica gel

(heptane/ethyl acetate). The appropriate fractions were collected and concentrated to give pure **4a**. Compound **4a** was dissolved in 30 mL CH_2Cl_2 and treated with BBr_3 (3.5 mmol). After 1 hour another 2.1 mmol of BBr_3 was added. After 1.5 hours the mixture was carefully poured into sat. $NaHCO_3$ (aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography on silica gel (toluene/ethyl acetate) afforded pure **4b** in 62% yield. (Rf = 0.50 toluene/ethyl acetate (4:1)); ESI-MS : M+H = 375.2, M-H = 373.0.

General procedure to prepare compounds ***5a-v*** *(10-aryl-2,8-dihydroxy-11H-benzo[b]fluorenes)*

(reference to scheme 3).

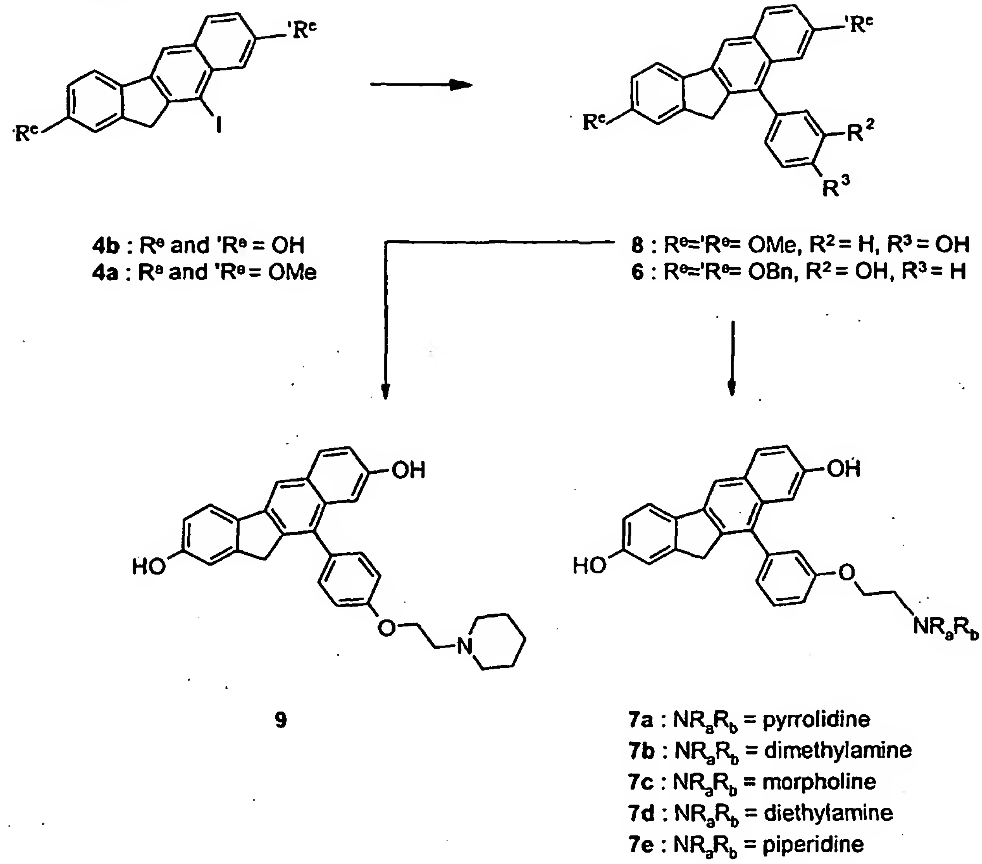
A mixture of 10-iodo-benzofluorene derivative **4** (27 μmol), 3 mg $Pd_2(dba)_3$, 0.2 M Na_2CO_3(aq), 30 μmol arylboronic acid and 1 ml 2-methoxy-ethanol was heated for 5 hours at 55^0 C. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (toluene/ethylacetate) to give pure **5a-v** (yields 14-52 %).

Compound	ARYL	Yield (%)	[M-H]
5a	4-chlorophenyl	37	[M-H] = 357.2
5b	2-naphthyl	44	[M-H] = 373.2
5c	3-methoxyphenyl	32	[M-H] = 353.4
5d	3-trifluoromethylphenyl	54	[M-H] = 391.3
5e	4-methylphenyl	42	[M-H] = 337.4
5f	3-chloro-4-fluorophenyl	40	[M-H] = 375.2
5g	3,4-methylenedioxophenyl	49	[M-H] = 367.4
5h	4-phenylphenyl	55	[M-H] = 399.4
5i	2-benzothiazole	30	[M-H] = 379.4
5j	3-fluorophenyl	27	[M-H] = 341.4
5k	4-methoxyphenyl	27	[M-H] = 353.4
5l	4-fluorophenyl	52	[M-H] = 341.4
5m	3,4-dichlorophenyl	14	[M-H] = 390.8
5n	3-chlorophenyl	37	[M-H] = 357.0
5o	4-trifluoromethylphenyl	22	[M-H] = 391.4
5p	3-methylphenyl	21	[M-H] = 337.2

5q	3-isopropylphenyl	40	[M-H] = 365.0
5r	4-trifluoromethyloxyphenyl	41	[M-H] = 407.2
5s	3-fluoro-4-phenylphenyl	22	[M-H] = 417.0
5t	4-methylthiophenyl	32	[M-H] = 371.2
5u	2-trifluoromethylphenyl	20	[M-H] = 391.0
5v	Phenyl	25	[M-H] = 323.2

Example 2

Scheme 4



Compound ***7a-d***

A mixture of **4b** (0.94 mmol), potassium carbonate (3.0 mmol) and benzyl bromide (2.1 mmol) in acetone (10 ml) was refluxed overnight after which the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (heptane/ethyl acetate).

The purified product (0.43 mmol) was taken up in 2-methoxyethanol (16 ml) and $Pd_2(dba)_3$ (36 μmol), 3-hydroxyphenylboronic acid pinacolester (0.45 mmol) and Na_2CO_3 (2M in water, 2 ml) were added. The mixture was stirred for 30 minutes at 60°C, poured into water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (CH_2Cl_2/methanol) to give pure **6** in 56% yield. (R_f = 0.34 (heptane/ethyl acetate (7:3)).

A mixture of **6** (48 µmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (76 µmol) and cesium carbonate (0.15 mmol) in acetonitrile (2 ml) was stirred for 3 hours at 50°C. The mixture was poured into water and extracted with ethyl acetate, the organic extract was dried over $MgSO_4$, the solvent evaporated and the residue was purified by chromatography on silica gel (CH_2Cl_2/methanol). The pure fractions were concentrated and the material obtained was dissolved in ethyl acetate (3 ml). Pd/C (10% w/w, 25 mg) and 3 drops of acetic acid were added and the mixture was stirred under an atmosphere of hydrogen for 5 hours. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/methanol) to yield pure **7a** in 22% yield. Rf = 0.14 (CH_2Cl_2/methanol (9:1)), ESI-MS: M+H = 438.4, M-H = 436.2.

*Compound **7b***

Compound **7b** was prepared from **6** in 5% yield, in the same fashion as described for the preparation of **7a**, using 2-dimethylaminoethyl chloride hydrochloride (Rf = 0.18 CH_2Cl_2/methanol (9:1)); ESI-MS: M+H = 412.4, M-H = 410.4.

*Compound **7c***

Compound **7c** was prepared from **6** in 32% yield, in the same fashion as described for the preparation of **7a**, using 1-(2-chloroethyl)morpholine hydrochloride instead of 1-(2-chloroethyl)pyrrolidine hydrochloride (Rf = 0.21 CH_2Cl_2/methanol (9:1)); ESI-MS: M+H = 454.4, M-H = 452.2.

*Compound **7d***

Compound **7d** was prepared from **6** in 65% yield, in the same fashion as described for the preparation of **7a**, using 2-diethylaminoethyl chloride hydrochloride instead of 1-(2-chloroethyl)pyrrolidine hydrochloride (Rf = 0.17 CH_2Cl_2/methanol (9:1)); ESI-MS: M+H = 440.4, M-H = 438.2.

*Compound **7e***

Compound **7e** was prepared from **6** in 18% yield, as described for the preparation of **7a**, using 1-(2-chloroethyl)piperidine hydrochloride instead of 1-(2-chloroethyl)pyrrolidine hydrochloride (Rf = 0.15 CH_2Cl_2/methanol (9:1)); ESI-MS: M+H = 452.4, M-H = 450.2.

Compound **9**

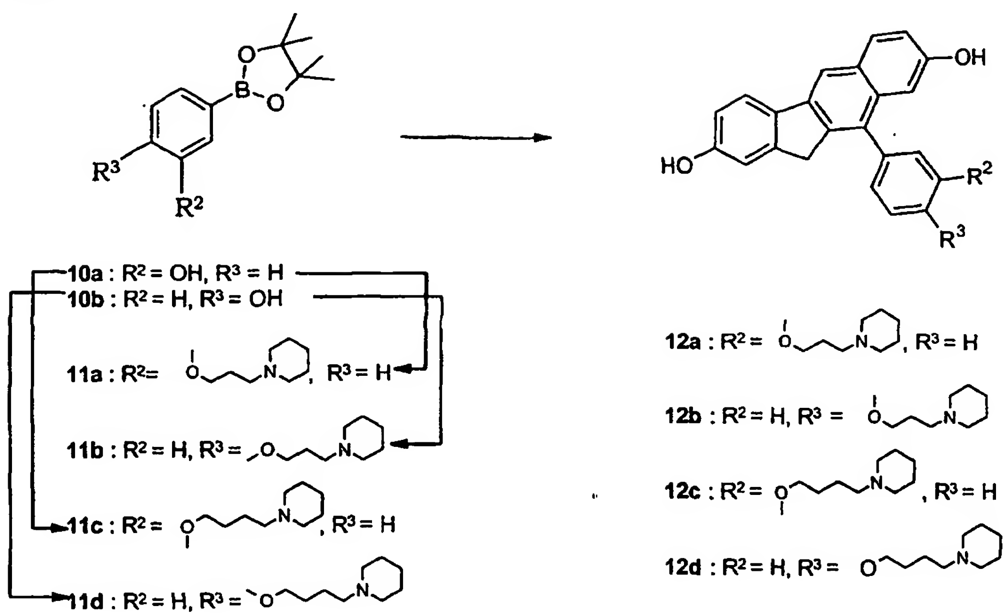
A mixture of **4a** (0.30 mmol), $Pd_2(dba)_3$ (0.40 μmol), 4-hydroxyphenylboronic acid (0.30 mmol) and sodium carbonate (2 M in water, 4 ml) in 12 ml 2-methoxyethanol was stirred at 60°C. After 30 minutes the mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (toluene/ethyl acetate) to give **8** in 65% yield. Rf = 0.24 (toluene/ethyl acetate (8:2)).

Compound **8** (0.16 mmol) was dissolved in toluene (3 ml). Sodium hydride (0.4 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.2 mmol) were added and the mixture was refluxed for 3.5 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (toluene/methanol).

The pure fractions were collected and concentrated, the material obtained (46 μmol) was dissolved in CH_2Cl_2 and treated with ethanethiol (0.62 mmol) and aluminum chloride (95 μmol) at RT. After 16 hours the dark red mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (CH_2Cl_2/methanol) to give **9** in 22% yield. Rf = 0.23 (toluene/methanol (85:15)), ESI-MS : M+H = 452.4, M-H = 450.2.

Example 3

Scheme 5



*Compound **12a***

A mixture of 3-hydroxyphenylboronic acid pinacolester **10a** (0.68 mmol), cesium carbonate (0.68 mmol) and 1-bromo-3-chloropropane (0.80 mmol) in acetonitrile (3 ml) was stirred overnight at RT. Additional cesium carbonate (0.31 mmol) and 1-bromo-3-chloropropane (0.4 mmol) were added and the mixture was stirred overnight at 60°C. The mixture was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2-layer was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (toluene/ethyl acetate). The purified product was dissolved in piperidine and stirred for 48 hours at 45°C. The solid material (piperidine.HCl) was filtered off and the filtrate was concentrated to give **11a** in 88% yield. Rf = 0.05 (toluene/ethyl acetate (4:1)).

A mixture of **4b** (67 μmol), **11a** (86 μmol), $PdCl_2(dppf)_2$ (5 μmol) and sodium carbonate (2 M in water, 0.25 ml) in 2.5 ml 2-methoxyethanol was stirred at 90°C. After 2 hours the mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (CH_2Cl_2/methanol). The appropriate fractions were collected and

concentrated, the material obtained was recrystallised from $CHCl_3$ to give **12a** in 38% yield. Rf = 0.42 (CH_2Cl_2/methanol (85:15)).

*Compound **12b***

A mixture of 4-hydroxyphenylboronic acid pinacolester **10b** (0.68 mmol), potassium hydroxide (2.1 mmol) and 1-bromo-3-chloropropane (2.8 mmol) in methanol (2 ml) was refluxed for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (toluene/ethyl acetate). The purified product was dissolved in piperidine and stirred overnight at 50°C. The solid material (piperidine.HCl) was filtered off and the filtrate was concentrated to give **11b** in 80% yield. Rf = 0.10 (toluene/methanol (9:1)).
Compound **12b** was prepared from **4a** and **11b** in 20% yield, in a similar fashion as described for the preparation of **12a**. Rf = 0.42 (CH_2Cl_2/methanol (85:15)), ESI-MS : M+H = 466.4, M-H = 464.6

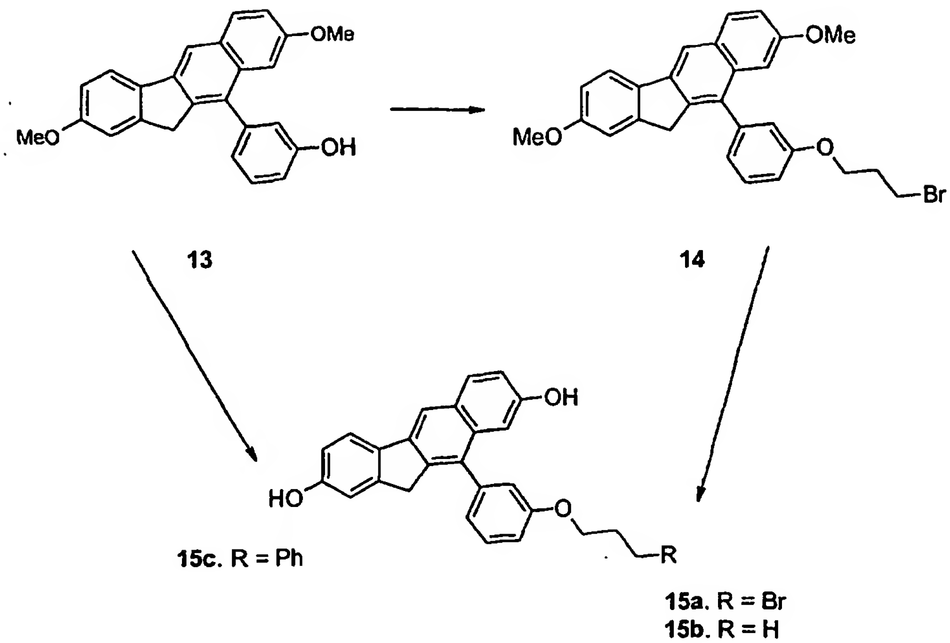
*Compound **12c***

Compound **12c** was prepared from **10a** in 25% yield, as described for the preparation of **12a**, using 1-bromo-4-chloro-butane instead of 1-bromo-3-chloro-propane. Rf = 0.21 (CH_2Cl_2/methanol (8:2)), ESI-MS : M+H = 480.6, M-H = 478.2

*Compound **12d***

To mixture of 1,4-diiodobutane (5 mmol) and cesium carbonate (0.68 mmol) in acetonitrile (2 ml) was portionwise added 4-hydroxyphenylboronic acid pinacolester **10b** (0.68 mmol) at 40°C. After 2.5 hours water was added and the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (heptane/toluene). The purified product was dissolved in piperidine and stirred at RT for 2 hours. The solid material (piperidine.HI) was filtered off and the filtrate was concentrated to give **11d** in 32% yield. Rf = 0.55 (toluene/methanol (8:2)).
Compound **12d** was prepared from **4b** and **11d** in 13% yield, in a similar fashion as described for the preparation of **12a**. Rf = 0.22 (CH_2Cl_2/methanol (8:2)), ESI-MS : M+H = 480.4, M-H = 478.2

Example 4
Scheme 6



Compound ***14***

A mixture of 2.03 mmole of 1,3-dibromopropane and 1.02 mmole of potassium carbonate in 10 ml of acetone was warmed to 40 °C. To this solution 0.51 mmole of **13** in 10 ml of acetone was added dropwise and the reaction mixture was stirred at 40 °C for 23 hours. An additional mixture of 2.03 mmole of 1,3-dibromopropane and 1.02 mmole of potassiumcarbonate in 5 ml of acetone was added and the reaction mixture stirred for 4 hours at reflux temperature. The reaction mixture was taken up in ethyl acetate and water, washed with water and saturated NaCl solution, dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel (heptane/ethyl acetate) to give pure **14** in 65% yield.
Rf = 0.64 (heptane/diethylether (7:3))

Compound ***15a***

82 µmole of **14** was dissolved in 6 ml of dry CH_2Cl_2. 327 µmole of $BF_3.S(CH_3)_2$ was added and the solution was stirred at room temperature

for 16 hours. The reaction mixture was taken up in ethyl acetate, washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel (CH_2Cl_2/methanol) to give pure **15a** in 93% yield.
Rf = 0.47 (CH_2Cl_2/methanol (9:1))

*Compound **15b***

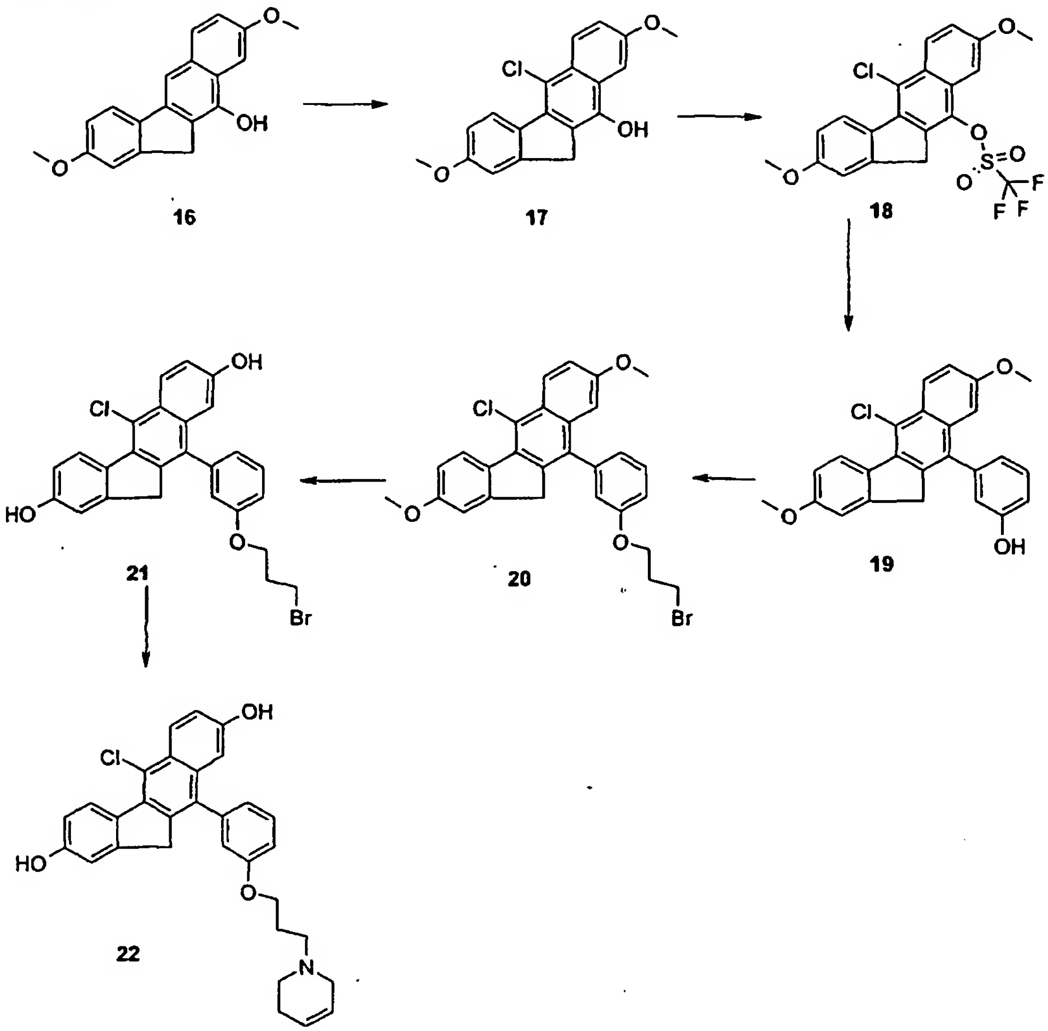
22 μM of bromide **14** was refluxed for 1.5 hours with 100 μM $LiAlH_4$ in THF. Water and ethyl acetate were added to the reaction mixture and the organic layer was separated, dried over $MgSO_4$ and concentrated.The residue was purified on silicagel (methylene/ methanol) to give pure 3'-O-propyl compound **15b** in yield 37%. Rf = 0.40 (heptane-ethyl acetate 7:3).

*Compound **15c***

54 μM of compound **13** was reacted with 1.7 mM 1-bromo-3-phenylpropane in the presence of 1.7 mM K_2CO_3 in 3 ml acetone at room temperature. After 24 hours the salts were removed by filtration. The filtrate was concentrated and redissolved in methylene chloride. The mixture was extracted with water, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (heptane/ ethylacetate). (yield= 88%).
47 μM of the resulting product was demethylated with 1.9 mM $(CH_3)_3S.BF_3$ in CH_2Cl_2 for one night. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (heptane / ethylacetate) to give pure compound **15c** in yield=57%. Rf 0.7 (heptane ethyl acetate 8:2)

Example 5

Scheme 7



*2,8-dimethoxy-10-hydroxy-11H-benzo[b]fluorene (Compound **16**)*

The compound 2,8-dimethoxy-10-hydroxy-11*H*-benzo[*b*]fluorene (Compound **16**) 1 was prepared from its corresponding ester as explained above for step 4 in scheme 1. An amount of 3 g of the corresponding unsaturated ester was added in small portions over a few minutes to 30 ml of methanesulphonic acid at 60ºC. After stirring for ½ hr the cyclization was complete. The mixture was then poured onto ice water and stirred for an additional ½ hr. The product was filtered, washed with water and thoroughly dried over P_2O_5, to give 2.2 gr of compound **16**.

R_f 0.38 (heptane / eth. ac. 7/3). NMR (DMSO) 3.82, 3.88 (2x3, s, OCH_3), 3.95 (s, 2, CH_2). 9.57 (s, 1, OH), 6.97, 7.11, 7.20, 7.55, 7.51, 7.75, 7.80 (7H's, aromatic protons)

*5-chloro-2,8-dimethoxy-10-hydroxy-11H-benzo[b]fluorene (Compound **17**)*

To a solution of 800 mg of compound **16** in 10 ml of DMF was added 850 mg of 2,2,3,4,5,6-hexachlorocyclohexa3,5-diene in small portions over 5 minutes. The mixture was stirred for 1 hr and then poured into 50 ml of water. The dark reaction product was extracted with ethyl acetate and purified by chromatography over silica gel (heptane / ethyl acetate as eluent), to provide 380 mg of **17** as a brown solid; R_f 0.38 (hept ./ ethyl ac. 6/4) , R_f (starting material) 0.44. NMR (DMSO) 3.85, 3.92 (2xs, 6, OCH_3) 4.03 (s, 2, CH_2), 7.03, 7.30, 8.13, 8.38 (2x AB, 4, Ar-H) , 7.25 , 7.61 (2x br.s, 2, Ar-H).

*Compound **18***

To a solution of 900 mg of **17** in 8 ml of pyridine was added at 0°C 700µl of trifluoromethanesulphonic anhydride. Stirring was performed for 1 hr at RT followed by pouring into water and additional stirring for 15 min. followed by filtration of the crude product. Purification was achieved by chromatography over silicagel, to provide 800 mg of triflate **18**; Mp 165-168°C. NMR ($CDCl_3$) 3.90 , 3.96 (2x s , 6 , OCH_3), 4.18 (s, 2, CH_2), 7.0, 7.09, 7.29, 7.35, 8.11, 8.47 (6H, Ar-H).

*Compound **19***

A mixture of 210 mg of triflate **18**, 220 mg of 3-hydroxyphenyl-pinacolborane, 200 mg of K_3PO_4, 15 mg of $As(PPh)_3$, 15 mg of $PdCl_2.PPh_3$, 0.5 ml of water and 5 ml of dioxane was heated at 100°C for 1,5 hr under a nitrogen atmosphere. The reaction was poured into water and extracted with ethyl acetate. Chromatography of the resulting material provided 215 mg of **19** as an amorphous product; R_f 0.35 (hept./ethyl ac. 7/3), Mp 184-185°C. NMR ($CDCl_3$) 3.74, 3.87 (s, 6, OCH_3), 3.80 (s, 2, CH_2) , 6.82-7.0 (m, 6, Ar-H), 7.25, 7.40, 8.38, 8.53 (4H, Ar-H).

*Compound **20***

A mixture of 200 mg of **19**, 500 mg of powdered K2CO3, 1.25 ml of 1,3-dibromopropane and 10 ml of acetonitrile was heated at 55°C for 3 hr.

The reaction was diluted with water and extracted with ethyl acetate. The crude product was purified by chromatography on silica gel (hept. / ethyl acetate) , to provide 220 mg of **20**; R_f 0.63 (hept./eth.ac. 7/3) ; NMR ($CDCl_3$) 3.65 (t,3, CH_2Br), 2.33 (m, 2, CH_2), 4.13 (t, 2, CH_2O), 3.78 (s, 2, CH_2).

*Compound **21***

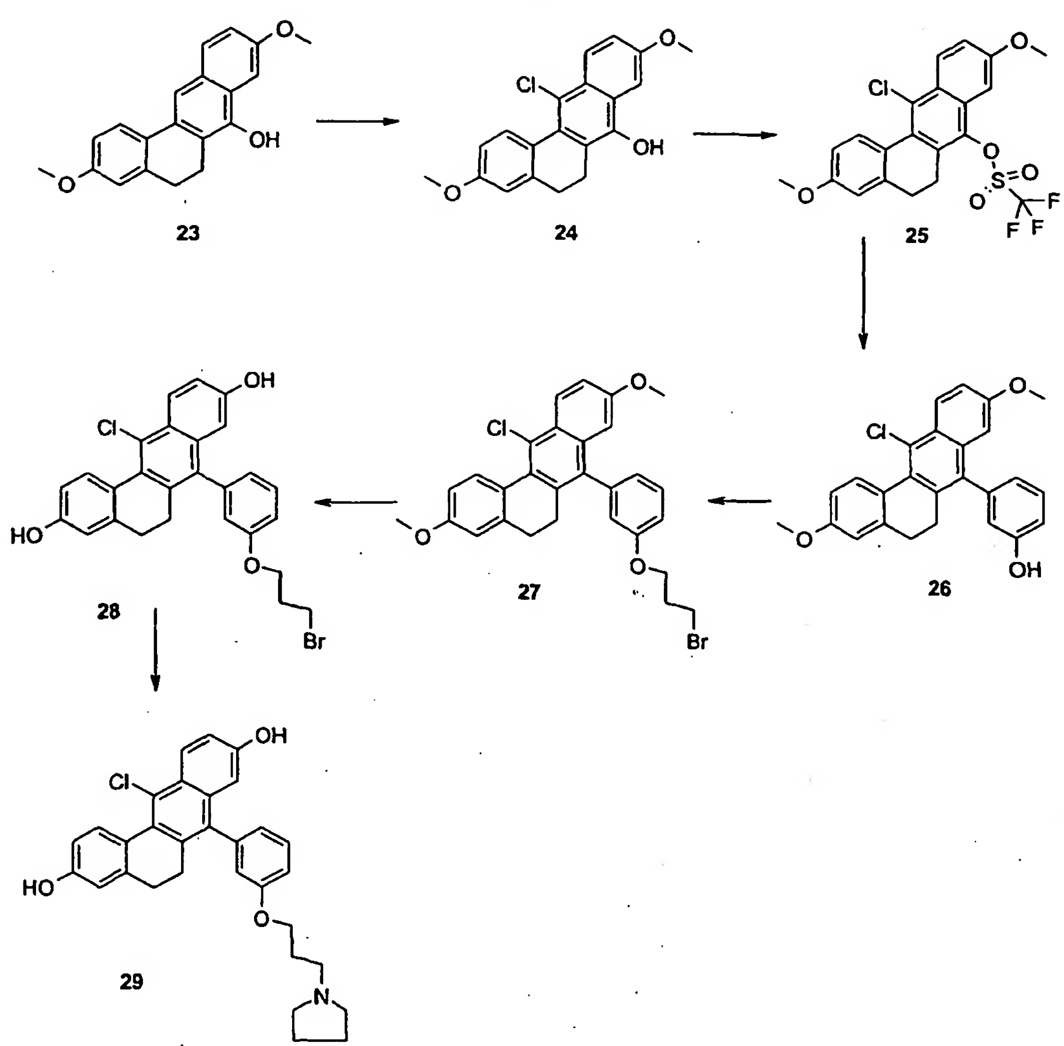
To a solution of 220 mg of **20** in 7 ml of methylenechloride was added 1.5 ml of BF_3.dimethylsulfide complex. The mixture was stirred until completion of the reaction (5 hr). The reaction was poured into water and the product extracted with ethyl acetate. Chromatography provided 210 mg of **21** as a colorles amorphous material; R_f 0.25 (hept./ eth.ac. 7/3) . NMR ($CDCl_3$) 3.67 (t,3, CH_2Br), 2.33 (m, 2, CH_2), 4.15 (t, 2, CH_2O), 3.77 (s, 2, CH_2).

*Compound **22***

A mixture of 70 mg of **21**, 0.3 ml of 1,2,5,6-tetrahydropyridine and 3 ml of acetonitrile was heated at 55^{0}C for ½ hr. The mixture was then poured onto 5% $NaHCO_3$ and extracted with ethyl acetate. The product was purified by passing through a short silica column (CH_2Cl_2/CH_3OH). The product thus obtained was converted into a HCl salt by treatment of a solution the free base in methanol/ether with 1M HCl/ether.The hydrochloride salt thus obtained was freeze-dried from water to obtain 45 mg of amorphous **22**. NMR (DMSO) 9.77 , 9.82 (2x s, 2, OH's), 5.70 and 5.88 (2x m, 2, tetrahydropyridine), 8.32, 8.20, 7.52, 7.21, 7.08, 6.98, 6.87 (10, aromatic H's).

Example 6

Scheme 8



*3,9-dimethoxy-7-hydroxy-5,6-dihydro-benz[a]anthracene (compounds **23**) and 12-chloro-3,9-dimethoxy-7-hydroxy-5,6-dihydro-benz[a]anthracene (compound **24**)*

The compound 3,9-dimethoxy-7-hydroxy-5,6-dihydro-benz[*a*]anthracene (compounds **23**) was prepared analogously to compound **16** in example 5. To a solution of 600 mg of **23** in 10 ml of DMF was added in portions 600 mg of 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dien-1-one. The mixture was then stirred at 40ºC for 4 hr. Then the reaction was poured into water and the product extracted with ethyl acetate. The crude material was passed through a silicagel column (hept./ eth.ac.) and finally triturated with heptane-diisopropyl ether to provide 280 mg of **24** as

orange crystals; Mp 140-141^{0}C, R_f 0.28 (hept./eth.ac. 7/3) starting material R_f 0.30.

Compound **25**

To a solution of 300 mg of **24** in 3 ml of pyridine was added 200 µl of triflic anhydride . The mixture was stirred for 1 hr at rt, and then poured into water and extracted with ethyl acetate.. The product was purified over silica gel and afforded 220 mg of **25** as a white solid; Mp 122-124; R_f 0.70 (hept./ethyl ac. 7/3).

Compound **26**

A mixture of 210 mg of **25**, 220 mg of 3-hydroxyphenylpinacolborane, 200 mg of K_3PO_4 15 mg of $(PPh_3)As$, 15 mg of $PdCl_2(PPh_3)_2$, 0.5 ml of water and 5 ml of dioxane was heated at 100^{0}C for 1.5 hr.The mixture was then poured into water and extracted with ethyl acetate. Chromatography over silica gel provided 215 mg of **26** as an oil; R_f 0.28 (hept. / ethyl acetate 7/3) . NMR (DMSO) 2.56 (4, CH_2CH_2), 3.67, 3.80 (2x s, 6, OCH_3), 8.32, 8.18, 7.33, 6.93,6.70 (10, Ar-H's) , 9.64 (s, 1, OH).

Compound **27**

A mixture of 215 mg of **26**, 500 mg of K_2CO_3 , 1.2 ml of 1,3-dibromopropane and 10 ml of acetonitrile was heated at 55^{0}C for 2.5 hr. The reaction was then poured in water and extracted with ethyl acetate. Chromatography provided 220 mg of **27** as a colorles oil ; R_f 0.60 (hept./ethyl acetate 7/3) . NMR ($CDCl_3$) 2.60 (m, 4, CH_2CH_2), 2.30 (m, 2, CH2), 3.60 (t,2, CH_2Br) , 4.13 (t,2, CH_2O) ,3.72, 3.87 (2x s, 6, OCH3).

Compound **28**

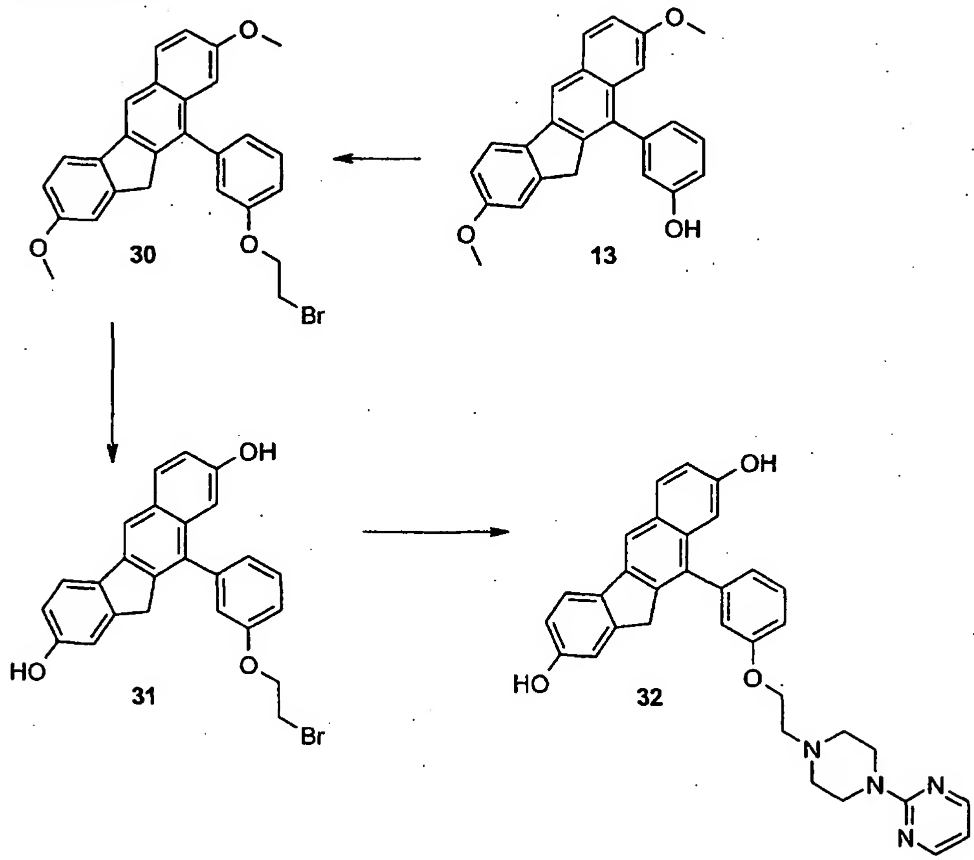
To a solution of 190 mg of **27** in 7 ml of methylenechloride was added 1.5 ml of BF_3.dimethylsulfide complex. After stirring at rt for 4 hr the mixture was poured onto water and extracted with ethyl acetate. Chromatography of the crude product gave 150 mg of essentially pure **28**; R_f 0.20 (hept./ ethyl ac. 7/3); NMR (DMSO) 2.27 (m, 2, CH2), 2.50 (m, 4, CH_2CH_2), 3.68 (t, 2, CH_2Br), 4.12 (t, 2, CH_2O), 9.68, 9.82 (2xs, 2, OH).

Compound **29**

A mixture of 60 mg of **28**, 0.4 ml of pyrrolidine and 3 ml of acetonitrile was stirred at 50°C for ½ hr . The ixture was then poured into 5% NaHCO3 and extracted with ethyl acetate. The product was purified by passing through a short silica column (CH_2Cl_2/CH_3OH as eluent) and then converted into a HCl salt by treatment with 1M HCl / ether. The resulting hydrochloride was freeze dried from water to give 35 mg of **29**; R_f 0.20 ($CH_2Cl_2/CH_3OH/HOAc$ 90/10/1); NMR (DMSO) 9.70 and 9.82 (2x s, 2H, OH's), 8.22, 8.05, 7.48 7.17, 7.06, 6.88, 6.84, 6.76, 6.70, 6.62 (m, 10H, Ar-H's), 4.10 (t,2, CH_2O).

Example 7

Scheme 9



*Compound **30***

A mixture of 300 mg of compound **13**, 900 mg of powdered K_2CO_3, 2 ml of 1,2-dibromopropane and 8 ml of acetonitrile was heated at 55°C for 16

hr. The reaction was diluted with water and extracted with ethyl acetate. The crude product was purified by chromatography on silica gel (hept. / ethyl acetate), to provide 310 mg of **30**; R_f 0.50 (hept./eth.ac. 7/3) ; NMR ($CDCl_3$) 3.67 (t,3, CH_2Br), 4.35 (t, 2, CH_2O), 3.79 (s, 2, CH_2), 3.75, 3.87 (2x s, 6, OCH_3).

*Compound **31***

To a solution of 310 mg of **30** in 6 ml of methylenechloride was added 2 ml of BF_3.dimethylsulfide complex. The mixture was stirred until completion of the reaction (5 hr). The reaction was poured into water and the product extracted with ethyl acetate. Chromatography provided 290 mg of **31** as a colorles amorphous material; R_f 0.19 (hept./ eth.ac. 7/3) . NMR ($CDCl_3$) 3.67 (t,3, CH_2Br),), 4.35 (t, 2, CH_2O), 3.76 (s, 2, CH_2).

*Compound **32***

A mixture of 60 mg of **31** 0.3 g of 2-pyrimidinylpiperazine and 2 ml of acetontrile was heated at 50°C for 16 hr. The mixture was then diluted with water and the product extracted with ethyl acetate. The organic material was passed through a short silica column (a gradient of CH_2Cl_2 / CH_3OH as eluent), to provide essentially pure **32** as the free base. This was dissolved in a small amount of ethyl acetate and treated with 1M HCl in ether to give the HCl salt. This was freeze dried from water to provide 48 mg of amorphous HCl salt of **32**. R_f 0.82 (CH_2Cl_2-CH_3OH- acetic acid 9/1/0,1) ; NMR (DMSO) 4.50 (m , 2, CH_2O), 6.76 , 6.84, 6.88, 6.96, 7.05, 7.09, 7.16, 7.21 ,7.55, 8.21, 8.32, 8.44 (resp. 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 1H, 2H's ; Ar-H's).

Example 8

Biological activity

Determination of competitive binding to cytoplasmic human estrogen receptor α or β from recombinant CHO cells is used to estimate the relative affinity (potency ratio) of a test compound for estrogen receptors present in the cytosol of recombinant Chinese hamster ovary (CHO) cells, stably transfected with the human estrogen receptor α (hERα) or β receptor (hERβ), as compared with 17β-estradiol (E_2).

The estrogenic and antiestrogenic activity of compounds is determined in an in vitro bioassay with recombinant Chinese hamster ovary (CHO) cells stably co-transfected with the human estrogen receptor α (hERα) or β receptor (hERβ), the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC). The estrogenic activity (potency ratio) of a test compound to stimulate the transactivation of the enzyme luciferase mediated via the estrogen receptors hERα or hERβ is compared with the standard estrogen estradiol. The antiestrogenic activity (potency ratio) of a test compound to inhibit the transactivation of the enzyme luciferase mediated via the estrogen receptors hERα or hERβ by the estrogen estradiol is compared with the standard ICI 164.384 (= (7α,17β)-N-butyl-3,17-dihydroxy-N-methylestra-1,3,5(10)-triene-7-undecanamide).

Results

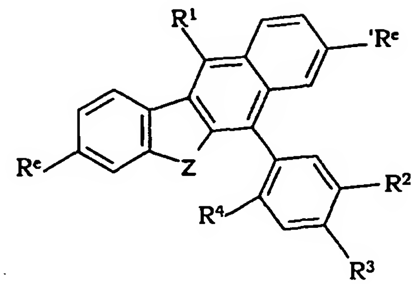
Compound	ERβ antagonism
5a	+
5b	+
5c	+
5d	+
5e	++
5f	+
5g	+
5h	+
5I	+
5j	+
5k	+
5l	++
5m	++
5n	+
5o	+
5p	+
5q	+
5r	++

Compound	ERβ antagonism
5s	+
5t	+
5u	++
5v	+
7a	+++
7b	+++
7c	+++
7d	+++
7e	+++
9	++
12a	+++
12b	++
12c	+++
12d	+
14	++
17a	+++
17b	++
17c	++

> 5% (relative to ICI): +
> 40% : ++
> 100%: +++

Claims

1. A compound having the formula 1



Formula 1

wherein:

R^e and $'R^e$ are OH, optionally independently etherified or esterified;

Z is $-CH_2-$ or $-CH_2CH_2-$;

R^1 is H, halogen, CF_3, or (1C-4C)alkyl;

R^2, R^3 and R^4 are independently H, halogen, $-CF_3$, $-OCF_3$, (1C-8C)Alkyl, hydroxy, (1C-8C)alkyloxy, aryloxy, aryl(1C-8C)alkyl, halo(1C-8C)alkyl, $-O(CH_2)_mX$, wherein X is halogen or phenyl and m = 2-4; $-O(CH_2)_mNR_aR_b$, $-S(CH_2)_mNR_aR_b$ or $-(CH_2)_mNR_aR_b$, wherein m = 2-4 and R_a, R_b are independently (1C-8C)alkyl, (2C-8C)alkenyl, (2C-8C)alkynyl, or aryl, optionally substituted with halogen, $-CF_3$, $-OCF_3$, $-CN$, $-NO_2$, $-OH$, (1C-8C)alkoxy, aryloxy, carboxyl, (1C-8C)alkylthio, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl or R_a and R_b form a 3-8 membered ring structure, optionally substituted with halogen, $-CF_3$, $-OCF_3$, $-CN$, $-NO_2$, hydroxy, hydroxy(1C-4C)alkyl, (1C-8C)alkoxy, aryloxy, (1C-8C)alkylthio, carboxyl, carboxylate, (1C-8C)alkyl, aryl, aryl(1C-8C)alkyl, halo(1C-8C)alkyl.

2. A compound according to claim 1, characterised in that Z is $-CH_2-$ and R^4 is H.

3. A compound according to claim 1 or 2, characterised in that R^1 is H, halogen or CF_3.

4. A compound according to anyone of claims 1-3, characterised in that R^1 is halogen.

5. A compound according to claim 2, characterised in that
R^1 is H;
R^3 is H;
R^2 is (3C-6C)alkyloxy, $-O(CH_2)_mX$, wherein X is halogen or phenyl and m = 2-3, or $-O(CH_2)_mNR_aR_b$, wherein m = 2-3 and R_a, R_b are independently (1C-5C)alkyl or (3C-5C)alkenyl, optionally substituted with OH or methoxy, or R_a and R_b form a 4-7 membered ring structure selected from the list: azetidine, pyrrolidine, 3-pyrroline, piperidine, piperazine, tetrahydropyridine, morpholine, thiomorpholine, thiazolidine, homopiperidine, tetrahydroquinoline and 6-azabicyclo[3.2.1]octane, which 4-7 membered ring structure can optionally be substituted with OH, hydroxy(1C-2C)alkyl, methoxy, acetyl, carboxylate, (1C-3C)alkyl, phenyl, benzyl, and phenylethyl.

6. A compound according to any one of claim 1-5 for use as a medicine

7. The use of a compound according to any one of claims 1-5 for the manufacture of a medicine for use in estrogen-receptor related treatments.

8. A pharmaceutical composition comprising a compound according to anyone of claim 1-6

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 01/09500

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C321/28 C07C43/23 C07C39/24 C07C39/21 C07D295/08
C07C217/16 C07D317/54 C07D277/66 C07C43/215 A61K31/136
A61K31/05 A61K31/085 A61K31/40 A61K31/4453 A61P5/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2001	13/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/09500

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/70 C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of box C.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/09500

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